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Sleep, cardiac autonomic function, and carotid atherosclerosis in patients with cardiovascular risks: HSCAA study

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ABSTRACT

Objectives: Behavioral and psychosocial factors have been gaining increased attention in regard to cardiovascular diseases. We evaluated sleep conditions, cardiac autonomic function, and carotid atherosclerosis in subjects who participated in the Hyogo Sleep Cardio-Autonomic Atherosclerosis (HSCAA) Study.

Methods: This cross-sectional study included 330 serial patients registered in the HSCAA study who were free from past cardiovascular diseases, and prescribing α- or β-blockers. In addition to clinical background and classical cardiovascular risk factors, sleep efficiency, apnea hypopnea index (AHI), awake physical activity, heart rate variability (HRV), carotid intima-media thickness (IMT), presence of plaque and plaque score were determined.

Results: Sleep efficiency ($r = -0.183$) and all HRV parameters (SDNN: $r = -0.202$; rMSSD: $r = -0.234$; pNN50: $r = -0.277$) were significantly ($p < 0.01$) and negatively associated with IMT, while AHI ($r = 0.220$, $p < 0.001$) was positively associated with IMT. Similarly, sleep efficiency ($r = -0.129$), HRV parameters (SDNN: $r = -0.170$; rMSSD: $r = -0.217$; pNN50: $r = -0.260$) and AHI ($r = 0.184$) were also significantly ($p < 0.05$) associated with plaque scores. Multivariate logistic regression analyses showed that rMSSD, but not sleep efficiency or AHI, was significantly associated with carotid plaque (OR 0.74, 95% CI 0.56-0.98, $p = 0.037$), independent of classical risk factors. The association of rMSSD with carotid plaque remained significant even after adjustment for sleep efficiency or AHI. A comparison of risk factors in specific subgroups showed that the association of lower HRV with carotid plaque was more prominent in patients with cardiovascular risk factors including male gender, hypertension, dyslipidemia and diabetes mellitus.

Conclusion: Cardiac autonomic nervous dysfunction was independently associated with carotid atherosclerosis, independent of sleep condition. Moreover, that association was more prominent in specific subgroups with cardiovascular risk factors.

1. Introduction

The importance of behavioral and psychosocial factors for prevention, development, and treatment of cardiovascular disease (CVD) has been increasingly recognized in the medical and scientific communities [1–4]. Sleep is one of the most important behavioral factors that may be involved in occurrence of CVD [5–8]. However, limited studies have shown an association between sleep and mortality using objectively recorded sleep duration [9]. Potential mechanisms associated with behavioral and psychosocial factors include autonomic nervous function. Autonomic nervous dysfunction has been shown to be associated with a higher incidence of cardiovascular events [10,11].

Carotid intima-media thickness (IMT) is a surrogate marker of arterial thickness [12], and it has become established as a predictor of cardiovascular events [13,14]. No reports of the relationship

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between quantitatively measured sleep conditions and carotid atherosclerosis have been presented, while only a limited number of studies examined the relationship between HRV and IMT in specified groups of patients [15–17]. Particularly, none have systematically measured quantitative sleep conditions, cardiac autonomic function, and carotid IMT together with confounding cardiovascular risk factors to thoroughly examine their mutual relationships.

In the present study, we cross-sectionally investigated mutual relationships among sleep conditions, cardiac autonomic function, and IMT in 330 patients with cardiovascular risk factors.

2. Methods

2.1. Study design and participants

This cross-sectional study was conducted from October 2010 to January 2014 and included 330 registered patients who were part of the ongoing HSCAA Study, which was designed to examine the impacts of sleep, autonomic imbalance, and subclinical atherosclerosis on cardiovascular events. Patients with 1 or more cardiovascular risk factor(s) (obesity, smoking, presence of cardiovascular event history, hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease) were registered, and received examinations for anthropological data, cardiovascular risk factors, carotid atherosclerosis, pulse wave velocity, cardiac ultrasound, actigraph, apnea-hypopnea index, HRV, and ambulatory blood pressure monitoring. All agreed to participate in the study by providing written informed consent and the study was approved by the Ethics Committee of Hyogo College of Medicine (approval No. 948). The complete detailed study protocol is found in Supplementary Materials electronically provided.

2.2. Assessment of classical cardiovascular risk factors

We defined hypertension as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or treatment for hypertension. Dyslipidemia [18] and type 2 diabetes [19] was defined as previously described. Details are found in Supplementary Materials electronically provided.

2.3. Assessment of sleep disorder, sleep/awake condition

To examine the presence of a sleep disorder and sleep/awake condition, we used an Apnomonitor (SAS-2100®, Teijin, Tokyo, Japan) to determine apnea hypopnea index (AHI) and an Actigraph (Ambulatory Monitoring, Inc., Ardley, New York, USA), as previously described [20]. Sleep efficiency as a parameter of sleep condition was calculated as total sleep time divided by the time spent in bed [21]. We also measured awake physical activity, with higher values representing greater daytime physical activity.

2.4. Cardiac autonomic nervous function

HRV was used to noninvasively measure cardiac modulation by autonomic nervous activity as previously described [20]. We sequentially recorded HRV for 48 h, and the latter 24-h series of data from the 48-h recording was analyzed as described [20]. The standard deviation of the NN(RR) interval (SDNN), root mean square of the successive normal sinus NN interval differences (rMSSD), and mean percentage of successive NN interval differences >50 ms (pNN50) within the time domain were calculated. Detailed methods and reproducibility of the measurements are provided in Supplementary Materials.

2.5. Carotid ultrasonography

Measurements of carotid IMT and plaques [22,23], and plaque score [24] was measured as previously described. IMT was calculated by automatic readers (Intimascope, Media Cross, Tokyo, Japan) [25]. Carotid plaque was defined as the presence of plaque with an IMT equal to or greater than 1.5 mm, as previously described [22,23]. Plaque score, an index of plaque severity, was calculated by summing maximum thickness (IMT of 1.1 mm and up) at each of four divisions of both sides of the carotid arteries as previously [24]. Details of their measurements and reproducibility are provided in Supplementary Materials.

2.6. Statistical analysis

Pearson's correlation coefficient was used for determining correlations among the factors. To compare variables between groups, a non-repeated *t*-test and chi-square test were utilized. Multivariate logistic regression analyses were used to calculate odds ratio (OR) and 95% confidence interval (CI) values. All statistical analyses were performed using the Statistical Package for the Social Sciences software (PASW Statistics version 18.0). All reported p values are 2-tailed and were considered statistically significant at the <0.05 level. Detailed methods are provided in Supplementary Materials.

3. Results

The characteristics of the present subjects are shown in Table 1. Those with carotid plaque had greater age, percentage of males, percentage with hypertension, dyslipidemia and diabetes mellitus, and AHI, as well as lower sleep efficiency as compared to those without carotid plaque. All HRV parameters, i.e., ln (SDNN), ln (rMSSD), and ln (pNN50), were significantly lower in subjects with than without carotid plaque, while awake physical activities were not significantly different between those. In simple regression

Table 1
Clinical characteristics of subjects (n = 330) and comparisons between with and without carotid plaque.

Variables	Total	Carotid plaque (−) (n = 212)	Carotid plaque (+) (n = 118)	P
Age, years	57.9 ± 13.9	53.0 ± 13.4	66.8 ± 10.1	<0.001
Male sex, n (%)	168 (50.9%)	90 (42.5%)	78 (66.1%)	<0.001
Body mass index, kg/m2	24.1 ± 4.4	24.3 ± 4.5	23.7 ± 4.1	0.217
Current smoking, n (%)	82 (24.8%)	49 (23.1%)	33 (28.0%)	0.328
Hypertension, n (%)	189 (57.3%)	102 (48.1%)	87 (73.7%)	<0.001
Dyslipidemia, n (%)	188 (57.0%)	112 (52.8%)	76 (64.4%)	0.042
Diabetes mellitus, n (%)	120 (36.4%)	63 (29.7%)	57 (48.3%)	0.001
Sleep/awake parameters				
AHI	9.0 ± 10.1	7.7 ± 9.8	11.3 ± 10.3	0.002
Sleep efficiency	89.9 ± 7.8	90.8 ± 7.6	88.2 ± 8.0	0.008
Awake physical activity	146.6 ± 36.7	144.8 ± 37.5	149.8 ± 35.1	0.255
HRV parameters				
ln (SDNN), msec	4.77 ± 0.30	4.82 ± 0.28	4.70 ± 0.32	0.001
ln (rMSSD), msec	3.14 ± 0.50	3.23 ± 0.50	2.97 ± 0.46	<0.001
ln (pNN50), msec	1.13 ± 1.50	1.44 ± 1.45	0.59 ± 1.42	<0.001
Carotid atherosclerosis				
IMT, mm	1.42 ± 0.74	0.98 ± 0.22	2.23 ± 0.68	<0.001
Plaque score	2.14 ± 2.33	0.87 ± 1.00	4.41 ± 2.33	<0.001

Data are presented as the mean ± standard deviation and n (%) for dichotomous variables. Three HRV parameters (SDNN, rMSSD, pNN50) were natural logarithm-transformed (ln) to achieve a normal distribution. P values are shown comparisons of means of 2 groups (unrepeated t-test) or percentages (Chi-square test). AHI: apnea hypopnea index, HRV: heart rate variability, SDNN: standard deviation of NN(RR) interval, rMSSD: root mean square of successive normal sinus RR interval differences, pNN50: mean percentage of successive NN interval differences >50 ms, IMT: intima-media thickness.

analyses, sleep efficiency was significantly associated with some of the HRV parameters (SDNN: r = 0.087, P = 0.134; rMSSD: r = 0.117, P = 0.045; pNN50: r = 0.130, P = 0.025). AHI was significantly and inversely correlated with all HRV parameters (SDNN: r = −0.202, P < 0.001; rMSSD: r = −0.118, P = 0.032; pNN50: r = −0.116, P = 0.036).

Fig. 1 presents the correlation coefficients between max IMT (Fig. 1-1) or plaque score (Fig. 1-2), and AHI, sleep efficiency, awake physical activity, and HRV parameters. Sleep efficiency, but not awake physical activity, was significantly and inversely associated with max IMT, AHI was significantly and positively associated with IMT, and HRV parameters were significantly and inversely associated with IMT. Similarly, sleep efficiency, AHI, and HRV parameters were significantly correlated with plaque scores.

To further analyze whether sleep condition and HRV parameters are independently associated with carotid plaque, stepwise multivariate logistic regression analyses were performed (Table 2). In the basic model, age, male gender, current smoker, and presence of hypertension, and dyslipidemia and diabetes were included as covariates, with current smoker, hypertension, dyslipidemia and diabetes not selected as significant covariates. When ln (AHI), sleep efficiency, awake physical activity, or an HRV parameter (rMSSD) was included as a covariate in the basic model, only rMSSD was significantly and inversely associated with occurrence of carotid plaque. When another HRV parameter was included as a covariate instead of rMSSD, pNN50, but not SDNN, was also significantly associated with the presence of carotid plaque (data not shown). A significant association between rMSSD and the presence of plaque was also observed when AHI, sleep efficiency, and awake physical activity were included as covariates (data not shown). Thus, cardiac autonomic dysfunction, but not sleep efficiency or AHI, was significantly and independently associated with carotid plaque.

Finally, logistic regression analyses of specific subgroups were performed to determine which groups of subjects had a more prominent association between HRV and the presence of carotid plaque (Table 3). Either ln (rMSSD) or ln (pNN50) was significantly and independently associated with the presence of plaque in patients with classical cardiovascular risk factors, including male gender, hypertension, dyslipidemia, and diabetes, while significant relationships were not observed with the opposite parameters, including female gender, and without hypertension, dyslipidemia, or diabetes. HRV parameters were also significantly and

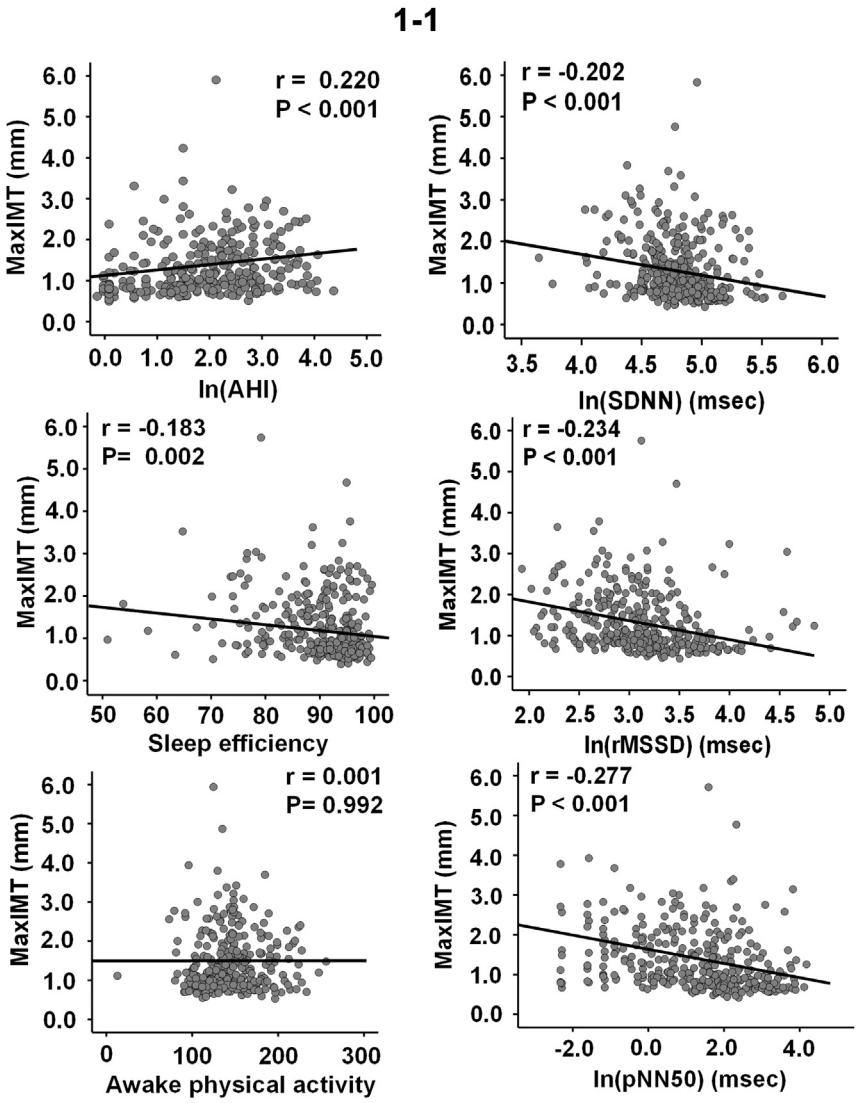

Fig. 1. Simple regression analyses between maximum IMT (Fig 1-1) or plaque score (Fig 1-2) and AHI, sleep efficiency, awake physical activity, and HRV parameters. AHI and HRV parameters were natural logarithm-transformed (ln) to achieve a normal distribution. IMT: intima-media thickness, HRV: heart rate variability, AHI: apnea hypopnea index.

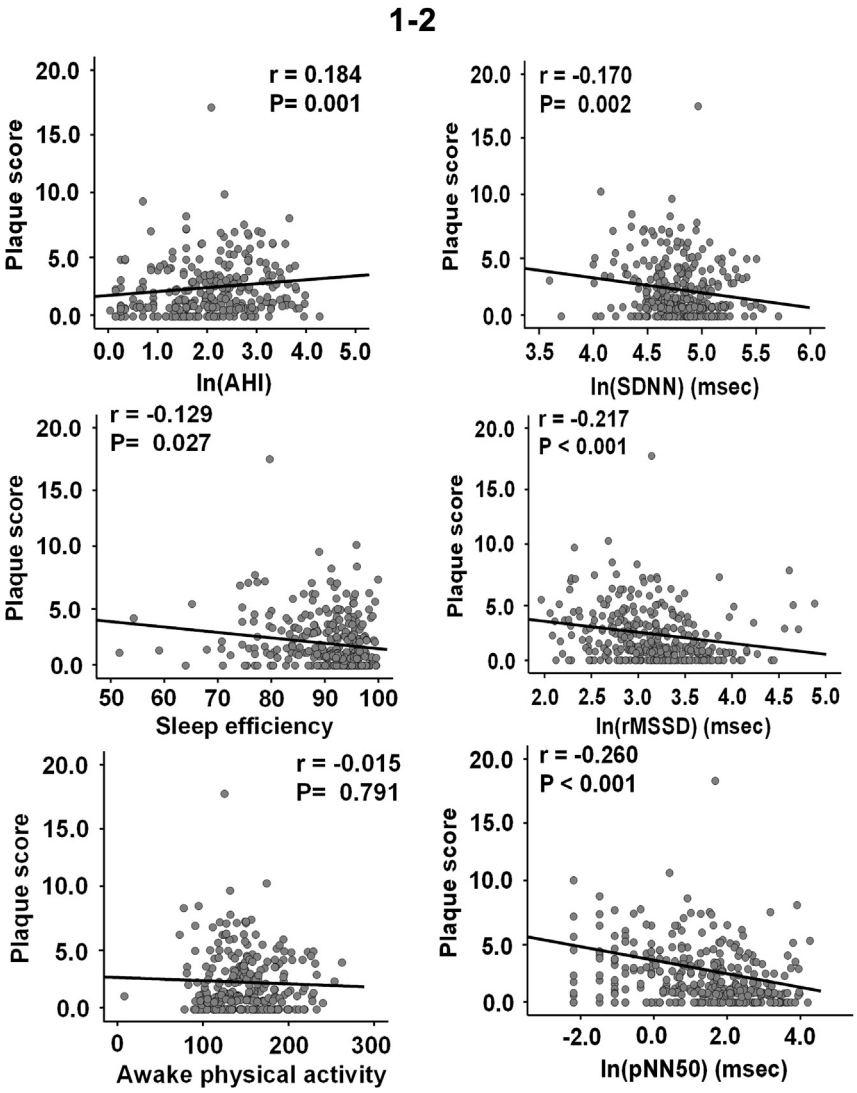

Fig. 1. (*continued*).

independently associated with the presence of carotid plaque in patients with lower age.

4. Discussion

This cross-sectional study is the first to systematically examine the relationships between these behaviors and psychosocial quantitative measures and atherosclerotic surrogate markers in patients with cardiovascular risk factors. In patients registered in the HSCAA study, we found that decreased cardiac autonomic function were significantly and independently associated with the presence of carotid plaque. The relationship was also independent of sleep quality and awake physical activity. We also found that the association was more prominent in specific subgroups of subjects with classical cardiovascular risk factors, including male gender, hypertension, dyslipidemia and diabetes mellitus.

In a previous study, self-reported long sleep duration in a Japanese population was significantly correlated with the incidence of carotid artery atherosclerosis [26]. Obstructive sleep apnea (OSA) has also been shown to be associated with increased carotid IMT [27,28]. In the present cohort, simple regression analysis showed that actigraphically measured sleep efficiency was significantly and inversely associated with carotid IMT, while AHI was also significantly associated with carotid IMT as well as the presence of plaque. However, those relationships were lost after adjustment for other cardiovascular risk factors in stepwise multiple logistic regression analyses. Thus, our results lie against the concept that sleep condition is independently associated with carotid atherosclerosis, rather suggest the associations may reflect co-morbid conditions, which can induce a decrease in sleep quality.

In contrast to sleep condition, the relationship between decreased HRV and carotid atherosclerosis was significant even after adjustment for classical cardiovascular risk factors. Furthermore, the association was significantly independent of sleep quality and awake physical activity. Thus far, only limited reports have shown a relationship between HRV and IMT, with the results obtained in specified groups of patients, including those with type 2 diabetes mellitus [15], hypertension [16], and depression [17]. Although HRV has been shown to be associated with various clinical factors including age, gender, and BMI in both healthy and diseased subjects [29–32], previous reports did not sufficiently examine the impact of confounding factors on the relationship between HRV and carotid atherosclerosis. To the best of our knowledge, the present study is the first to examine the

Table 2
Stepwise multiple logistic regression analyses of factors associated with presence of carotid plaque.

Variables	OR (95% CI)	P
Model 1		
Age (per 1 year)	1.10 (1.07–1.13)	<0.001
Male sex (female = 0, male = 1)	2.44 (1.43–4.15)	0.002
Nagelkerke R^2	0.355	<0.001
Model 2		
Age (per 1 year)	1.10 (1.07–1.13)	<0.001
Male sex (female = 0, male = 1)	2.44 (1.43–4.15)	0.009
ln (AHI) (per 1SD)	not selected	
Nagelkerke R^2	0.355	<0.001
Model 3		
Age (per 1 year)	1.10 (1.07–1.13)	<0.001
Male sex (female = 0, male = 1)	2.15 (1.22–3.80)	0.008
Hypertension (absence = 0, presence = 1)	1.68 (0.91–3.09)	0.092
Sleep efficiency (per 1SD)	not selected	
Nagelkerke R^2	0.382	<0.001
Model 4		
Age (per 1 year)	1.10 (1.07–1.13)	<0.001
Male sex (female = 0, male = 1)	2.18 (1.24–3.85)	0.007
Hypertension (absence = 0, presence = 1)	1.70 (0.92–3.12)	0.085
Awake physical activity (per 1SD)	not selected	
Nagelkerke R^2	0.384	<0.001
Model 5		
Age (per 1 year)	1.10 (1.07–1.13)	<0.001
Male sex (female = 0, male = 1)	2.33 (1.36–3.99)	0.002
ln (rMSSD) (per 1SD)	0.74 (0.56–0.98)	0.037
Nagelkerke R^2	0.369	<0.001

The Hosmer–Lemeshow goodness of fit p-value was significant for all models. Model 1 included age, male sex, current smoker, and presence of hypertension, dyslipidemia, and diabetes mellitus as covariates. In other models, ln(AHI) (Model 2), sleep efficiency (Model 3), awake physical activity (Model 4) or ln(rMSSD) (Model 5) was added to Model 1. AHI and rMSSD were natural logarithm-transformed (ln) to achieve a normal distribution. AHI: apnea hypopnea index, HRV: heart rate variability, rMSSD: root mean square of the successive normal sinus RR interval differences, SD: standard deviation, OR: odds ratio, CI: confidence interval.

Table 3
Associations of HRV parameters with presence of carotid plaque in specific subgroups.

Subgroup	Variables	OR (95% CI)	P	OR (95% CI)	P
Age		<61		≥61	
	ln (rMSSD) (per 1 SD)	0.49 (0.27–0.90)	0.021	0.83 (0.60–1.16)	0.291
	ln (pNN50) (per 1 SD)	0.52 (0.30–0.90)	0.019	0.88 (0.62–1.24)	0.474
Gender		Male		Female	
	ln (rMSSD) (per 1 SD)	0.59 (0.39–0.89)	0.012	0.94 (0.64–1.38)	0.772
	ln (pNN50) (per 1 SD)	0.57 (0.38–0.87)	0.010	1.02 (0.68–1.53)	0.889
Current smoking		Yes		No	
	ln (rMSSD) (per 1 SD)	0.76 (0.36–1.59)	0.478	0.77 (0.57–1.04)	0.097
	ln (pNN50) (per 1 SD)	0.72 (0.37–1.39)	0.333	0.81 (0.59–1.11)	0.203
Hypertension		Yes		No	
	ln (rMSSD) (per 1 SD)	0.67 (0.48–0.94)	0.022	0.91 (0.54–1.55)	0.743
	ln (pNN50) (per 1 SD)	0.66 (0.46–0.93)	0.020	1.05 (0.62–1.78)	0.844
Dyslipidemia		Yes		No	
	ln (rMSSD) (per 1 SD)	0.65 (0.45–0.95)	0.026	0.77 (0.46–1.30)	0.338
	ln (pNN50) (per 1 SD)	0.70 (0.49–1.01)	0.057	0.75 (0.45–1.27)	0.294
Diabetes Mellitus		Yes		No	
	ln (rMSSD) (per 1 SD)	0.58 (0.38–0.88)	0.011	0.92 (0.60–1.40)	0.704
	ln (pNN50) (per 1 SD)	0.52 (0.33–0.82)	0.005	1.03 (0.69–1.55)	0.859

Multiple logistic regression analyses were performed. The Hosmer–Lemeshow goodness of fit p-value for all models was significant. Covariates included age, male sex, current smoking, hypertension, dyslipidemia, diabetes mellitus, and one of the HRV parameters in each model. HRV parameters were natural logarithm-transformed (ln) to achieve a normal distribution. HRV: heart rate variability, rMSSD: root mean square of successive normal sinus NN interval differences, pNN50: mean percentage of successive NN interval differences >50 ms, OR: odds ratio, CI: confidence interval.

relationship between HRV and carotid atherosclerosis in patients with cardiovascular risk(s) after full adjustments for age, gender, and other classical atherosclerotic risk factors.

Our findings are also the first to show that the relationship between decreased cardiac autonomic function and subclinical carotid atherosclerosis is more prominent in patients with classical cardiovascular risk factors, including male gender, hypertension, dyslipidemia, and diabetes. Previously, there were no reports that showed the impact of gender on the relationship between HRV and IMT. Our analyses in specific subgroups are in good agreement with previous studies showing an association between HRV and IMT in patients with hypertension and those with diabetes mellitus [15,16]. Thus, our results suggest that the association of HRV with carotid atherosclerosis may be more pronounced in high-risk patients.

Because of the nature of the cross-sectional design of our study, it remains unclear if cardiac autonomic dysfunction is the cause of atherosclerosis or vice versa. Autonomic dysfunction has been shown to be associated with several risk factors for atherogenesis, including platelet aggregation [33], lipoprotein metabolism [34], and inflammatory cytokines [17,35]. In our analyses, relationship of autonomic dysfunction with IMT was independent of many of the risk factors for atherosclerosis. Autonomic dysfunction may also directly affect the arterial function via an alpha-adrenergic mechanism [36]. Despite of the impact on autonomic dysfunction on vascular bed and reports of vascular contribution to regulation of the autonomic function being limited, the reverse may also be true. In rabbits, removal of the endothelium increased the release of norepinephrine from sympathetic nerve terminals in carotid artery [37]. Recent intriguing report by Dutta et al. found that myocardial ischemia induces inflammation in atherosclerotic plaques via β3-adrenoceptor system, suggesting bidirectional role of autonomic nervous system in atherosclerotic diseases [38].

Our study has some limitations. First and most importantly, this study has a cross-sectional design, and thus, no causal relationship can be demonstrated by design, which has to be considered a major shortcoming of this trial. Second, even though the number of subjects was adequate to examine associations among factors, they may not be generalized for patients with cardiovascular risk factors. Nevertheless, our results provide an important first step to unveil the pathophysiological significance of sleep conditions and autonomic dysfunction in patients with atherosclerotic diseases. Ongoing follow-up examinations of our HSCAA cohort will potentially reveal the underlying mechanisms of the relationships of behavioral and psychosocial conditions with cardiovascular events.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2014.12.032.

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